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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RODERICK JOHN SCOTT

Appeal 2008-004077
Application 10/058,825
Technology Center 1600

Decided:[1] June 2, 2009

Before DEMETRA J. MILLS, FRANCISCO C. PRATS, and MELANIE L. McCOLLUM, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

STATEMENT OF CASE

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for indefiniteness, lack of written description and lack of enablement. We have jurisdiction under 35 U.S.C. § 6(b).

The following claims are representative.

20. A method for the production of modified endosperm, which comprises the step of introducing a nucleic acid molecule into a plant, the nucleic acid molecule comprising a promoter that targets expression to female germ line cells and a sequence whose transcription product comprises a partial or full-length *Arabidopsis* DNA methyltransferase 1 (Metl) sequence, wherein the introduced nucleic acid is effective for down-regulating one or more DNA methylating enzymes present in the plant, whereby the degree of DNA methylation of nucleic acid in the plant is reduced as compared to a control plant.

21. A method as claimed in claim 20 wherein the transcription product comprises an antisense nucleic acid.

62. A method for the production of modified endosperm, which comprises the step of introducing a nucleic acid molecule into a plant, the nucleic acid molecule comprising a promoter that targets expression to female germ line cells and a sequence whose transcription product comprises a partial or full-length *Z. mays* DNA sequence orthologous to the *Arabidopsis* DNA methyltransferase 1 (Metl) sequence, wherein the introduced nucleic acid is effective for down-regulating one or more DNA methylating enzymes present in the plant, whereby the degree of DNA methylation of nucleic acid in the plant is reduced as compared to a control plant.

63. A method as claimed in claim 62, wherein the transcription product comprises an antisense nucleic acid.

64. A method as claimed in claim 20, wherein the plant is a dicotyledonous plant.

65. A method as claimed in claim 20, wherein the transcription product down-regulates one DNA methylating enzyme.

66. A method as claimed in claim 20, wherein the transcription product comprises a full or partial sense copy of the *Arabidopsis* DNA methyltransferase 1 (Metl) sequence.

67. A method as claimed in claim 66, wherein the sense copy is a partial sense copy.

69. A method as claimed in claim 62, wherein the transcription product comprises a full or partial sense copy of the *Z. mays* sequence.

71. A method as claimed in claim 66, wherein the plant is a dicotyledonous plant.

76. A method as claimed in claim 62, wherein the plant is a dicotyledonous plant.

77. A method as claimed in claim 20, wherein the promoter targets expression in female gametic cells.

78. A method as claimed in claim 77, wherein the transcription product comprises an antisense nucleic acid.

80. A method as claimed in claim 77, wherein the transcription product comprises a partial sense copy of the *Arabidopsis* DNA methyltransferase 1 (Metl) sequence.

81. A method as claimed in claim 77, wherein the plant is a dicotyledonous plant.

82. A method as claimed in claim 77, wherein the plant is a monocotyledonous plant.

83. A method as claimed in claim 81, wherein the plant is a *Brassica* plant.

84. A method as claimed in claim 81, wherein the plant is a *B. napus* plant.

85. A method as claimed in claim 82, wherein the plant is a *Zea mays* plant.

86. A method as claimed in claim 62, wherein the promoter targets expression to female gametic cells.

87. A method as claimed in claim 86, wherein the transcription product comprises an antisense nucleic acid.

88. A method as claimed in claim 86, wherein the transcription product comprises a partial sense copy of the *Z. mays* sequence orthologous to *Arabidopsis* DNA methyltransferase 1 (Metl) sequence.

89. A method as claimed in claim 86, wherein the plant is a dicotyledonous plant.

90. A method as claimed in claim 86, wherein the plant is a monocotyledonous plant.

91. A method as claimed in claim 89, wherein the plant is a *Brassica* plant.

92. A method as claimed in claim 89, wherein the plant is a *B. napus* plant.

93. A method as claimed in claim 90, wherein the plant is a *Zea mays* plant.

Cited References

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van der Krol et al., *An anti-sense chalcone synthase gene in transgenic plants inhibits flower pigmentation*, 333 NATURE 866-869 (1988).

Carron et al., *Genetic modification of condense tannin biosynthesis in Lotus corniculatus. 1. Heterologous antisense dihydroflavonol reductase down-regulates tannin accumulation in "hairy root" cultures*, 87 THEORETICAL AND APPLIED GENETICS 1006-1015 (1994).

John W. Einset, *Differential expression of antisense in regenerated tobacco plants transformed with an antisense version of a tomato ACC oxidase gene*, 46 PLANT CELL TISSUE AND ORGAN CULTURE 137-141 (1996).

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Veena et al., *Glyoxalase I from Brassica juncea: molecular cloning regulation and its over-expression confer tolerance in transgenic tobacco under stress*, 17 THE PLANT JOURNAL 385-395 (1999).

Genbank Accession No AF063403 (1998).

Genbank Accession No AF007807 (1998).

Genbank Accession No AF034419 (1998).

Genbank Accession No AJ002140 (1998).

Cannon et al., *Organ-specific modulation of gene expression in transgenic plants using antisense RNA*, 15 PLANT MOLECULAR BIOLOGY 39-47 (1990).

Hibino et al., *Increase of Cinnamaldehyde Groups in Lignin of Transgenic Tobacco Plants Carrying an Antisense Gene for Cinnamyl Alcohol Dehydrogenase*, 59 BIOSEI. BIOTECH BIOCHEM 929-931 (1995).

Bolitho et al., *Antisense apple ACC-oxidase RNA reduces ethylene production in transgenic tomato fruit*, 122 PLANT SCIENCE 91-99 (1997).

Elkind et al., *Abnormal plant development and down-regulation of phenylpropanoid biosynthesis in transgenic tobacco containing a heterologous phenylalanine ammonia-lyase gene*, 87 PROC. NATL. ACAD. SCI. USA 9057-9061 (1990).

Salehuzzeman et al., *Isolation and characterization of a cDNA encoding granule-bound start synthase in cassava (manihot eculenta Crantz) and its antisense expression in potato,* 23 (5) PLANT MOL. BIOL. 947-962 (1993).

Grounds of Rejection

1. Claims 20-21, 62-67, 69, 71, 76-78, 80-93 stand rejected under 35 U.S.C. § 112, second paragraph.

2. Claims 20-21, 62-67, 69, 71, 76-78, 80-93 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement throughout the claim scope.

3. Claims 20-21, 62-67, 69, 71, 76-78, 80-93 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such away as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Discussion

1. Claims 20-21, 62-67, 69, 71, 76-78, 80-93 stand rejected under 35 U.S.C. § 112, second paragraph.

ISSUE

The Examiner argues that Appellant has disclosed that "the designation *Arabidopsis* Metl sequence will always refer to the sequence of Accession No. L 10692... (page 13 of Remarks filed 11/7/2005, 1st full paragraph)." (Ans. 3.) The Examiner finds that this sequence is a DNA sequence, therefore, it is unclear how a transcription product can be a

> DNA sequence and not a mRNA sequence. One skilled in the art knows transcription products are RNA molecules that may comprise non-translated regions, i.e., introns and 5' and 3' non-translated regions. In addition, the transcription product would be a mRNA molecule that is in reverse orientation from the strand from which it was transcribed. Therefore, the transcription product would not have the same sequence as the DNA sequence disclosed in Accession No. L10692.

(Ans. 3-4.)

Appellant contends that one of ordinary skill would understand what is claimed based on basic tenets of molecular biology, i.e., that the transcription product of an *Arabidopsis* Met1 sequence (or the Z. *mays*

ortholog) is an RNA sequence that is a faithful copy of the DNA template from which the transcription product was transcribed.

The issue is: Is the designation *Arabidopsis* Metl sequence of Accession No. L 10692 indefinite.

FINDINGS OF FACT

1. The Examiner finds that "Claim 20 is indefinite in the recitation 'a sequence whose transcription product comprises a partial or full length *Arabidopsis* DNA methyltransferase 1 (Metl) sequence.'" (Ans. 3.)

2. Appellant has disclosed that "the designation *Arabidopsis* Metl sequence will always refer to the sequence of Accession No. L 10692… (page 13 of Remarks filed 11/7/2005, 1st full paragraph)." *Id.*

3. The Examiner finds that the

> sequence is a DNA sequence, therefore, it is unclear how a transcription product can be a DNA sequence and not a mRNA sequence. One skilled in the art knows transcription products are RNA molecules that may comprise non-translated regions, i.e., introns and 5' and 3' non-translated regions. In addition, the transcription product would be a mRNA molecule that is in reverse orientation from the strand from which it was transcribed. Therefore, the transcription product would not have the same sequence as the DNA sequence disclosed in Accession No. L10692.

Id. at 3-4.

4. The Appellants argue that "one of ordinary skill would immediately understand that the DNA and RNA sequences of Accession No. L10692 are the same, with U (uracil) substituted for T (thymine)." (App. Br. 10.)

5. The Appellants argue that the "[r]eferences previously cited during prosecution to show that the designation *Arabidopsis* Met1 sequence refers to the sequence of Accession No. L10692 indicate that the DNA sequence of L10692 was itself derived from an RNA sequence." (App. Br. 10.)

6. A copy of Genbank Accession No. L10692 is of record, Evidence Appendix A. *Id.*

7. The Appellants argue that Finnegan states at page 2385, right-hand column that:

"The length of the methyltransferase cDNA assembled from the overlapping cDNA clones Yc8 and Yc2 is 4720bp not including a poly A tail (Accession No. L10692), which agrees with the estimate based on Northern analysis of 4.7kb (data not shown)." *Id.*

8. The Appellants argue that Finnegan

> [C]reated cDNAs from an *Arabidopsis* RNA, sequenced the cDNAs and deposited the resulting nucleotide sequence as Accession No. L10692. The results presented in the Finnegan et al article show that the sequence presented in Accession No. L10692 was derived from an RNA sequence and that the DNA and RNA sequences are the same, with U substituted for T. One of ordinary skill would immediately understand that the transcription product of Accession No. L10692 is an RNA that has the same sequence as L10692, with U substituted for T.

Id.

9. One of ordinary skill in the art at the time of filing of the present application would have been aware of the orthologous sequence of Zea Mays Met 1. (Genbank Accession No. AF063403 of record.)

10. Partial is defined as "incomplete" or "relating to only part" of something. *Webster's II New Riverside Dictionary*, Boston, Ma., p. 856 (1994).

PRINCIPLES OF LAW

With respect to the "indefiniteness" requirement 35 U.S.C. § 112, second paragraph, *Datamize LLC v. Plumtree Software Inc.*, 417 F.3d 1342, 1347-1348 (Fed. Cir. 2005) stated that

> According to the Supreme Court, "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." *United Carbon Co. v. Binney & Smith Co.,* 317 U.S. 228 . . . (1942). The definiteness requirement, however, does not compel absolute clarity. Only claims "not amenable to construction" or "insolubly ambiguous" are indefinite. *See Novo Indus., L.P. v. Micro Molds Corp.,* 350 F.3d 1348, 1353 (Fed.Cir.2003); *Honeywell Int'l,* 341 F.3d at 1338; *Exxon Research & Eng'g Co. v. United States,* 265 F.3d 1371, 1375 (Fed.Cir.2001). Thus, the definiteness of claim terms depends on whether those terms can be given any reasonable meaning. Furthermore, a difficult issue of claim construction does not *ipso facto* result in a holding of indefiniteness. *Exxon Research & Eng'g,* 265 F.3d at 1375. "If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds."

Id.

ANALYSIS

The Examiner finds that the *Arabidopsis* Metl Genbank Accession No. L 10692 sequence is a DNA sequence, and that it is unclear how a transcription product can be a DNA sequence and not a mRNA sequence. (Ans. 4.) The Examiner argues that

> One skilled in the art knows transcription products are RNA molecules that may comprise non-translated regions, i.e., introns and 5' and 3' non-translated regions. In addition, the

> transcription product would be a mRNA molecule that is in reverse orientation from the strand from which it was transcribed. Therefore, the transcription product would not have the same sequence as the DNA sequence disclosed in Accession No. L10692.

(Ans. 4.)

Appellant contends that "one of ordinary skill would understand what is claimed based on basic tenets of molecular biology, i.e., that the transcription product of an *Arabidopsis* Met1 sequence (or the Z. *mays* ortholog) is an RNA sequence that is a faithful copy of the DNA template from which the transcription product was transcribed." (App. Br. 10.)

We find that the Examiner has not established a prima facie case of indefiniteness or shown that reasonable efforts at claim construction of *Arabidopsis* Met1 prove futile. The Examiner has not shown that one of ordinary skill in the art, upon reading the present Specification would not have understood that the phrase "*Arabidopsis* Metl sequence" refers to the sequence of Genbank Accession No. L10692 described in the Specification and of record. Reasonable efforts to review references cited during prosecution show that the designation *Arabidopsis* Met1 sequence refers to the sequence of Genbank Accession No. L10692 and the Genbank Accession No. L10692 deposit information sheet indicates that the DNA sequence of L10692 was itself derived from a mRNA sequence. (FF 6-8.)

In view of the above, the indefiniteness rejection is reversed.

Claim 62

The Examiner finds that claim 62 is indefinite in the recitation "'a sequence whose transcription product comprises a partial or full length *Zea*

mays sequence orthologous to the *Arabidopsis* methyltransferase 1 (Metl) sequence.'" (Ans. 4.)

The Examiner argues that

> One skilled in the art knows transcription products are RNA molecules that may comprise nontranslated regions, i.e., introns and 5' and 3' non-translated regions. In addition, the transcription product would be a mRNA molecule that is in reverse orientation from the strand from which it was transcribed. Therefore, the transcription product would not have the same sequence as the DNA sequence disclosed in Accession No. L10692 . . . and because Accession No. L10692 is the Arabidopsis sequence and not the Zea mays sequence.

(Ans. 4.)

Appellant acknowledges that claim 62 is rejected for indefiniteness for essentially the same reasons that claim 20 was rejected. (App. Br. 9.) Therefore, we reverse the rejection of claim 62 for the same reasons indicated herein for the reversal of the indefiniteness rejection of claim 20. With respect to the *Zea mays* Met1 sequence, we find that one of ordinary skill in the art at the time of filing of the present application would have been aware of the *Zea mays* Met 1 orthologous to Arabidopsis Met1. (Genbank Accession No. AF063403 of record.) We further find that one of ordinary skill in the art would have understood that "partial sequences" of Met 1 refers to incomplete sequences of Met1, i.e., less than the full length sequence of Met1. In view of the above, we reverse the indefiniteness rejection of claim 62.

2. Claims 20-21, 62-67, 69, 71, 76-78, 80-93 stand rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

ISSUE

> The Examiner finds that the Specification is
>
> [E]nabling for a method for increasing the amount of endosperm in an *Arabidopsis* or *Brassica* seed or increasing the weight of an *Arabidopsis* or *Brassica* seed comprising a construct comprising a full length METl DNA sequence operably linked to the AGLS promoter, wherein the sequence is in antisense orientation, or wherein the METl DNA sequence is isolated by RT-PCR from *Arabidopsis* using the primers MET1F of SEQ ID NO: 5 and MET1R of SEQ ID NO: 6 and *Arabidopsis* and Brassica plant transformation therewith.

(Ans. 7.)

> However, the Examiner finds that the Specification
>
> [D]oes not reasonably provide enablement for claims broadly drawn to a method of modifying the endosperm from **any** plant comprising downregulating any DNA methylating enzyme using a sequence whose transcription product comprises a partial or full length *Arabidopsis* Metl sequence or which comprises a **partial** or full-length *Zea mays* sequence orthologous to the *Arabidopsis* Metl sequence, or wherein the nucleic acid is a partial or full length sequence in sense or antisense orientation.

Id. [Emphasis added.]

Appellant contends that the Jacobsen Declaration of record points out that the data in the Fourgoux-Nicol article indicate the *Arabidopsis* Met1 sequence would hybridize to and therefore down regulate a heterologous sequence in any plant. (App. Br. 25.)

The issue is: Does the Specification enable a method of modifying the endosperm from **any plant** comprising downregulating any DNA

methylating enzyme using a sequence whose transcription product comprises a partial or full length *Arabidopsis* Metl sequence.

FINDINGS OF FACT

11. The Examiner finds that the Specification

> [D]oes not reasonably provide enablement for claims broadly drawn to a method of modifying the endosperm from **any plant** comprising downregulating any DNA methylating enzyme using a sequence whose transcription product comprises a partial or full length *Arabidopsis* Metl sequence or which comprises a partial or full-length *Zea mays* sequence orthologous to the *Arabidopsis* Metl sequence, or wherein the nucleic acid is a partial or full length sequence in sense or antisense orientation.

(Ans. 7.)

12. The Examiner finds that the claims are not only drawn to decreasing overall methylation in a plant, but are drawn to decreasing methylation which results in production of a modified or altered endosperm development (Final Rej. 8). According to the Specification, pages 1 and 16, one example of a modified endosperm is a larger, heavier endosperm.

13. The Examiner finds that a method of modifying the endosperm from **any plant** is not supported by an enabling disclosure taking into account the *Wands* factors.

14. With respect to the *Wands* factors, the Examiner finds that Appellant "discloses cloning a sequence that encodes the *Arabidopsis* MET1 protein, wherein the nucleic acid sequence is 4.7kb long, in which the sequence was isolated by RT-PCR from an *Arabidopsis* cDNA library using the METlF primer of SEQ ID NO: 5 and METl R primer of SEQ ID NO:6." (Ans. 8.)

15. The Examiner agrees that Appellant "discloses subcloning the nucleic acid sequence into a vector comprising the AGL5 or AP3 promoter in antisense orientation (page 30, Example 3; and Figures 6 and 7) and *Arabidopsis,* Brassica campestris and Brassica oleraceae transformation therewith (page 31, Example 4, page 33, Example 5). Plants expressing the pAGL5Met1 as construct produced seed with increased weight (page 31, lines 26-28)." (Ans. 8.)

16. The Examiner finds that the state-of-the-art teaches down-regulating methylating genes produces unpredictable results. (Ans. 9.) To support this position, the Examiner relies on Jacobsen (2000) which teaches "transforming ***Arabidopsis*** with a nucleic acid encoding the MET1 protein operably linked to a promoter in antisense orientation caused a decrease in methylation by 80%-90%." (Ans. 9) (emphasis added.) Jacobsen also discloses that "'[s]urprisingly,… the floral development gene SUPERMAN, was ectopically ***hypermethylated*** [emphasis added] and silenced' (page 180, left column, 1st full paragraph)" (Ans. 9).

17. The Examiner finds that "Appellant has only disclosed primer sequences to be used for isolating the full length *Arabidopsis* MET1 sequence from an *Arabidopsis* cDNA library (See pages 30-31, Example 3a)." (Ans. 10.)

18. The Examiner further finds that "Appellant has not disclosed how one makes or isolates any of the other sequences that are encompassed by Appellant's broad claims." (Ans. 10.)

19. The Examiner finds that Appellant has not

> [T]aught which regions of the respective polynucleotides can be used to amplify, for example, the *Zea Mays* orthologous sequence, or which regions can be used as a probe to isolate any

> of said polynucleotide sequences whose transcription product comprises a partial *Arabidopsis* or *Zea mays* Met1 sequence that is effective for downregulating one or more DNA methylating enzymes present in the plant and produce a plant whose seeds produce modified endosperm.

Id.

20. The Examiner also finds that "[u]sing DNA sequences to reduce expression of the endogenous corresponding gene through the mechanism of sense suppression produces unpredictable results." (Ans. 10.) For example, Gutterson "teaches that the chrysanthemum and petunia chalcone synthase (CHS) genes are 70% identical to each other, and that transforming petunia plants with the chrysanthemum CHS gene did not co-suppress the endogenous petunia CHS gene (page 965, left column, second paragraph). Gutterson reports similar data using another petunia gene in the anthocyanin pathway." (Ans. 10.)

21. Regarding the state-of-the-art, the Examiner finds that the art teaches that "antisense molecules that exhibit less than 100% sequence identity to the target sequence produce unexpected results." (Ans. 10.) To support this position, the Examiner relies on Emery which "discloses experiments in which a target sequence of a micro-RNA was changed by two base-pairs. The altered base-pairs caused the complementary micro-RNA not to bind to the target sequence, which subsequently led to an increased expression of the target sequence's encoded protein (page 1769, right column, 2nd full paragraph)." (Ans. 10-11.)

22. "Finnegan … discloses that there are three classes of methyltransferases in *Arabidopsis*, METI, METII and METIII (page 228, top paragraph) and homology between METI and METII is higher in the methyltransferase domain than in the amino-terminal domain (sentence bridging pages 227-

228)." (Ans. 18-19.) Finnegan (1998) states "There is evidence supporting the notion that plant methyltransferases may differ in target specificity" (page 229, bottom paragraph).

23. The Examiner finds Appellant has not described essential regions of the MET1 sequence that can be used to down regulate a methyltransferase in a plant so that the plant produces seeds with the expected phenotype." (Ans. 19) (Emphasis added.)

24. The Examiner concludes that the

> [A]bsence of guidance, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified sequences, either by using non-disclosed fragments of a nucleic acid encoding the *Arabidopsis* Metl protein as probes or by designing primers to undisclosed regions of a nucleic acid encoding the *Arabidopsis* Met1 protein and isolating or amplifying fragments, subcloning the fragments, producing expression vectors and transforming plants therewith, in order to identify those, if any, that when over-expressed in female germ line cells down-regulate one or more DNA methylating enzymes present in a plant and produce a plant whose seeds produce a modified endosperm.

(Ans. 11.)

25. Jacobsen Declaration

Appellant puts forth the Declaration of Dr. Jacobsen as evidence of predictability and lack of undue experimentation in the relevant art.

26. Cannon

Dr. Jacobsen concludes that one of ordinary skill would have understood from Cannon that "a 41-base pairing homology was sufficient to give up to a 100% inhibition of GUS [gene] expression." Cannon 46. Jacobsen Declaration at ¶ 11.

The Cannon reference also states at page 39 that "antisense RNA has a complementary sequence to mRNA and inhibits gene translation by a mechanism as yet unknown but presumed to involve duplex formation."

27. Jacobsen and Finnegan

According to Dr. Jacobsen, the Jacobsen 2000 reference concerned

> [T]he observation that the *AGAMOUS* gene was hypermethylated in an *Arabidopsis* line expressing a Metl antisense construct. These lines were previously described as having up to a 90% decrease in overall DNA methylation. Finnegan et al., (1996) Proc. Natl. Acad. Sci. U.S.A. 93:8449. An earlier publication, the Jacobsen 1997 reference, showed that the *SUPERMAN* gene was hypermethylated in the same *Arabidopsis* line expressing a Metl antisense construct, and these experiments also confirmed the simultaneous overall hypomethylation in this line. (Jacobsen et al., Science 1997 277: 1100- 1103).

Jacobsen Declaration at ¶12.

28. The Jacobsen Declaration indicates that the "observation of hypermethylation of the *SUPERMAN* gene or the *AGAMOUS* gene in *Arabidopsis* Metl antisense construct-containing lines does not change the fact that these lines had a significant reduction in the degree of overall DNA methylation." Jacobsen Declaration at ¶ 14.

29. Dr. Jacobsen further concluded that the

> [T]echniques required to screen and identify Metl downregulation construct-containing plants that have a decrease in DNA methylation would have been routine for one of ordinary skill, because the techniques involved would have been typical of those carried out by one of ordinary skill. Such techniques include constructing DNA clones containing partial and full-length *Arabidopsis* or *Zea mays* DNA methyltransferase 1 Metl sequences, constructing plant

> transformation vectors, transforming plants, and screening for overall DNA methylation status.

Jacobsen Declaration at ¶ 16.

30. Dr. Jacobsen does not address how to predictably alter the phenotype of the endosperm or seed in any plant or evidence that methyltransferase is present in the endosperm of any plant.

31. Fourgoux-Nicol

According to Dr. Jacobsen, Fourgoux-Nicol shows that hybridization techniques were used successfully to isolate desired clones. Jacobsen Declaration at ¶ 18. Dr. Jacobsen finds that

> The authors of the Fourgoux-Nicol reference focused their analysis on one of the thirteen cDNA clones whose expression was strictly confined to the male gametophyte and was high in the microspore. The selected clone was designated M3 and had a length of 497 bp. Fourgoux- Nicol at page 863, left-hand column. M3 was used in a second round of screening by stringent hybridization to isolate a second cDNA clone, designated M3.21. M3.21 has a length of 674 bp. Fourgoux-Nicol at page 863, left-hand column. M3 and M3.21 were sequenced and found to have non-identical sequences, including a 99 base pair insertion in M3 that was not present in M3.21, and several single nucleotide polymorphisms between the two. Fourgoux-Nicol at page 863, right-hand column, and page 862 Figure 2. Further analysis, including Southern hybridization, indicated that the M3 and M3.21 cDNAs were derived from two homologous genes. Fourgoux-Nicol at page 864, left-hand column. Thus, the reference shows that 100% sequence identity is not required in order to successfully isolate related sequences by nucleic acid hybridization.

Jacobsen Declaration at ¶ 19.

32. Dr. Jacobsen concludes that

> The fact that nucleic acids that do not have 100% DNA sequence identity, such as M3 and M3.21, can hybridize to each other would indicate to one of ordinary skill that hybridization would likely occur between a partial or full length *Arabidopsis* or *Zea mays* DNA methyltransferase 1 Metl sequence and an endogenous DNA methyltransferase 1 Metl target even when there is less than 100% sequence identity.

Jacobsen Declaration at ¶ 20.

33. Hibino

Dr. Jacobsen finds that Hibino report that "introduction of an *Aralia cordala* cinnamyl alcohol dehydrogenase (CAD) antisense construct into tobacco resulted in an approximately 20-55% reduction in CAD activity. See page 929 and Figure 1 of Hibino." Jacobsen Declaration at ¶ 22.

Two plants showed a reduction in CAD whereas others showed no significant change, evidencing unpredictability in the art. (Hibino, page 929, col.2.)

34. Bolitho

Bolitho report that introduction of an apple antisense ACC-oxidase reduced the level of RNA and the activity of the corresponding gene for ethylene production in tomato. *See* Figures 3 and 4 of Bolitho. Jacobsen Declaration at ¶ 22.

35. Bolitho states that high levels of antisense sequence were not always associated with reduction in ethylene levels evidencing unpredictability in the art. (Abstract.)

36. Salehuzzaman

Salehuzzaman report that introduction of a cassava granule bound starch synthase antisense gene suppressed levels of the corresponding

protein in potato. *See* Figure 10 in Salehuzzaman. Jacobsen Declaration at ¶ 22.

In Salehuzzaman the gene in question was abundantly expressed in tubers (not endosperm), minimally expressed in petioles and stems and not expressed in roots. (Salehuzzaman, page 955.) Levels of antisense inhibition varied from complete inhibition to no visible effect, evidencing unpredictability in the art. (Salehuzzaman, page 960, col. 2.)

37. Elkind

Elkind report that introduction of a bean phenylalanine ammonia-lyase (PAL) sense sequence into tobacco resulted in reduced levels of PAL activity and reduced accummulation of endogenous PAL transcripts. *See* Elkind at page 9059-9060. Jacobsen Declaration at ¶ 22.

Dr. Jacobsen concluded that one of ordinary skill would have expected that, in general, heterologous partial or full length sequences can be used to downregulate endogenous genes based on, inter alia, the successful results reported in the references of paragraph 22, including Elkind.

38. Elkind concludes that transgenic plants can evidence a series of unusual, i.e., unexpected phenotypes, evidencing unpredictability in the art. (Abstract.) Expression of phenotype is also affected by the environment. (Elkind, page 9059.)

39. Emery

Emery looked at the function of HD-ZIP and KANADI genes in the meristem of plants with respect to adaxial and abaxial leaf production. The authors found five class III HDZIP genes in Arabidopsis and that they have diversified common and unique functions. (Emery 1771, col. 2.) Jacobsen Declaration at ¶ 25. Dr. Jacobsen concluded that one of ordinary skill, after

reviewing the Emery reference, would not conclude that use of antisense techniques in plant molecular biology requires a 100% sequence match between an introduced sequence and its target.

While the Emery reference reports that mismatches introduced within microRNA target sites can abolish mRNA function, such a result does not mean that sequences with imperfect homology would necessarily be ineffective for downregulation. Jacobsen Declaration at ¶ 25.

40. Gutterson

Dr. Jacobsen found after reviewing the Gutterson reference, that one of ordinary skill

> would not conclude that use of sense suppression techniques in plant molecular biology requires a 100% sequence match between an introduced sequence and its target. While the Gutterson reference reports that a chrysanthemum chalcone synthase sense sequence did not suppress a petunia chalcone synthase, such a result does not mean that sequences with imperfect homology would necessarily be ineffective for downregulation.

Jacobsen Declaration at ¶ 27.

41. Gutterson discloses that the proportion of plants with high levels of suppression decreased with decreasing fragment length. (Gutterson 965, col. 2.)

42. The complete carrot, corn, pea and tomato Metl sequences were known from the earliest priority date from Genbank Accession Numbers AF007807, AF063403, AF034419 and AJ002140. Evidence Appendices G, F, H, and I.

43. Appellant argues that there are numerous regions in carrot, corn, pea and tomato Metl sequences that are highly conserved even though *Zea mays* is a monocot and the remainder are dicots, directing one of ordinary skill to

partial *Arabidopsis* Metl sequences that would have been effective for downregulation in heterologous species. (App. Br. 19-20.)

44. "Applicant submitted eight additional references that report downregulation using heterologous sequences, including sequences having less than 100% sequence identity to an endogenous gene. Evidence Appendix N."[2]

45. According to Appellants, "[t]hese other prior art references show one of ordinary skill would have concluded that antisense sequences with less than 100% sequence identity can be used to downregulate a heterologous endogenous gene." (App. Br. 34.)

46. Oliver discloses that the production of heterologous hydroxypyruvate reductase (HPR) RNA did not systematically reduce levels of tobacco HPR. (Oliver, Abstract.)

47. VanderKrol discloses that the pattern of plant pigmentation derived from the flavonoid biosysnthesis pathway varies among flowers of different transgenic plants indicating that the antisense gene is influenced by DNA sequences that border the site of insertion in both a quantitative and qualitative way. (VanderKrol, Abstract.)

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[2] Temple, et al. Mol. Gen. Genet Vol. 236(3): pp. 3 15-325(1993); Oliver, M.J., et al. Mol. Gen Genet, Vol. 239(2): pp. 425-434 (1993); Van der Krol, A.R., et al., Nature Vol. 333: pp. 866-869 (1988); Canon, et al. Theoretical and Applied Genetics Vol. 87(8): pp. 1006- 10 15 (1994); Einset, J.W., Plant Cell Tissue and Organ Culture Vol. 46(2): pp. 137- 14 1 (1 996); Trevanion, et al. Plant Phvsiol. Vol. 1 13(4): pp. 1 153-1 165 (1997); Faske, et al. **Plant** Physiol. Vol. 1 15(2): pp. 705-7 15 (1 997); Herbik, et al. Eur. J. Biochem. 265(1): pp. 23 1-239 (1999); Veena, et al. Plant Journal 17(4): pp. 385-395 (1999).

48. Carron indicates that downregulation of tannin biosynthesis is dependent upon Lotus genotype. (Carron, Abstract.)

49. Einset discloses that there is differential expression of antisense genes involving ethylene production. Ethylene production in flowers was not effected but ethylene production in fruits was inhibited. (Einset, Abstract.)

PRINCIPLES OF LAW

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the **full scope** of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993) (emphasis added). In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *Wright*, 999 F.2d at 1561-1562.

Enablement is a question of law, based on underlying findings of fact. *See, e.g., In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23 (Fed. Cir. 1991), quoted *in Enzo Biochem, Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1372.

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the

> predictability or unpredictability of the art, and (8) the breadth of the claims.

Wands. 858 F.2d at 737.

"Patent protection is granted in return for an enabling disclosure . . . , not for vague intimations of general ideas that may or may not be workable." *Genentech*, 108 F.3d at 1366. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, *reasonable detail* must be provided in order to enable members of the public [skilled in the art] to understand and carry out the invention." *Id.* (emphasis added).

"[S]ufficient disclosure . . . to teach those of ordinary skill in the art how to make and how to use the invention . . . . means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *In re Vaeck*, 947 F.2d 488, 496, (Fed Cir 1991). A claim that covers many inoperative embodiments may be non-enabled. *Genentech Inc. v. The Wellcome Foundation Ltd.*, 29 F.3d 1555, 1560 (Fed. Cir. 1994).

The evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992) ("After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument."). A preponderance of the evidence exists when it suggests that it is more likely

than not that the assertion in question is true. *Herman v. Huddleston*, 459 U.S. 375, 390 (1983).

ANALYSIS

The Examiner argues that the claims are not enabled for at least two reasons. The first reason is that the Appellant's Specification does not enable the use of the claimed method in any plant. (Ans. 7.) The second reason is that the Appellant's Specification does not enable partial sequences of Arabidopsis Met1. (Ans. 7.) We will focus primarily on the first reason. The Examiner contends that the Specification

> [D]oes not reasonably provide enablement for claims broadly drawn to a method of modifying the endosperm from **any plant** comprising downregulating any DNA methylating enzyme using a sequence whose transcription product comprises a partial or full length *Arabidopsis* Metl sequence or which comprises a partial or full-length *Zea mays* sequence orthologous to the *Arabidopsis* Metl sequence, or wherein the nucleic acid is a partial or full length sequence in sense or antisense orientation.

(Ans. 7.) In particular, the Examiner finds that the claims are not only drawn to decreasing overall methylation in a plant, but are drawn to decreasing methylation which results in production of a modified or altered endosperm development (Final Rej. 8). Thus, the Examiner argues that a method of modifying the endosperm from **any plant** is not supported by an enabling disclosure taking into account the *Wands* factors.

With respect to the *Wands* factors, the Examiner finds that Appellant "discloses cloning a sequence that encodes the *Arabidopsis* MET1 protein, wherein the nucleic acid sequence is 4.7kb long, in which the sequence was

isolated by RT-PCR from an *Arabidopsis* cDNA library using the METlF primer of SEQ ID NO: 5 and METl R primer of SEQ ID NO:6." (Ans. 8.)

The Examiner agrees that Appellant "discloses subcloning the nucleic acid sequence into a vector comprising the AGL5 or AP3 promoter in antisense orientation (page 30, Example 3; and Figures 6 and 7) and *Arabidopsis,* Brassica campestris and Brassica oleraceae transformation therewith (page 31, Example 4, page 33, Example 5). Plants expressing the pAGL5Met1 as construct produced seed with increased weight (page 31, lines 26-28)." (Ans. 8.)

However, the Examiner finds that the state-of-the-art teaches down-regulating methylating genes produces unpredictable results. (Ans. 9.) To support this position, the Examiner relies on Jacobsen (2000) which teaches "transforming ***Arabidopsis*** with a nucleic acid encoding the MET1 protein operably linked to a promoter in antisense orientation caused a decrease in methylation by 80%-90%." (Ans. 9) (emphasis added.) Jacobsen also discloses that "'[s]urprisingly,… the floral development gene SUPERMAN, was ectopically ***hypermethylated*** [emphasis added] and silenced' (page 180, left column, 1st full paragraph)" (Ans. 9).

The Examiner finds that "Appellant has only disclosed primer sequences to be used for isolating the full length *Arabidopsis* MET1 sequence from an *Arabidopsis* cDNA library (See pages 30-31, Example 3a)." The Examiner further finds that "Appellant has not disclosed how one makes or isolates any of the other sequences that are encompassed by Appellant's broad claims." (Ans. 10.) Nor has Appellant

> [T]aught which regions of the respective polynucleotides can be used to amplify, for example, the *Zea Mays* orthologous sequence, or which regions can be used as a probe to isolate any

> of said polynucleotide sequences whose transcription product comprises a partial *Arabidopsis* or *Zea mays* Met1 sequence that is effective for downregulating one or more DNA methylating enzymes present in the plant and produce a plant whose seeds produce modified endosperm.

Id.

The Examiner also finds that "[u]sing DNA sequences to reduce expression of the endogenous corresponding gene through the mechanism of sense suppression produces unpredictable results." (Ans. 10.) For example, Gutterson "teaches that the chrysanthemum and petunia chalcone synthase (CHS) genes are 70% identical to each other, and that transforming petunia plants with the chrysanthemum CHS gene did not co-suppress the endogenous petunia CHS gene (page 965, left column, second paragraph). Gutterson reports similar data using another petunia gene in the anthocyanin pathway." (Ans. 10.)

Regarding the state-of-the-art, the Examiner finds that the art teaches that "antisense molecules that exhibit less than 100% sequence identity to the target sequence produce unexpected results." (Ans. 10.) To support this position, the Examiner relies on Emery which "discloses experiments in which a target sequence of a micro-RNA was changed by two base-pairs. The altered base-pairs caused the complementary micro-RNA not to bind to the target sequence, which subsequently led to an increased expression of the target sequence's encoded protein (page 1769, right column, 2nd full paragraph)." (Ans. 10-11.)

The Examiner asserts that Appellant has not indicated which regions of MET1 are specific to the methyltransferases of the instant invention. (Ans. 18-19.) The Examiner argues that "Finnegan … discloses that there are three classes of methyltransferases in *Arabidopsis*, METI, METII and

METIII (page 228, top paragraph) and homology between METI and METII is higher in the methyltransferase domain than in the amino-terminal domain (sentence bridging pages 227-228)." (Ans. 18-19.) Finnegan (1998) states "There is evidence supporting the notion that plant methyltransferases may differ in target specificity" (page 229, bottom paragraph). Therefore, the Examiner asserts, Appellant has not described essential regions of the MET1 sequence that can be used to down regulate a methyltransferase in a plant so that the plant **produces seeds with the expected phenotype**." (Ans. 19) (Emphasis added.)

> In sum, the Examiner concludes that the
>
> [A]bsence of guidance, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified sequences, either by using non-disclosed fragments of a nucleic acid encoding the *Arabidopsis* Metl protein as probes or by designing primers to undisclosed regions of a nucleic acid encoding the *Arabidopsis* Met1 protein and isolating or amplifying fragments, subcloning the fragments, producing expression vectors and transforming plants therewith, in order to identify those, if any, that when over-expressed in female germ line cells down-regulate one or more DNA methylating enzymes present in a plant and produce a plant whose seeds produce a modified endosperm.

(Ans. 11.) Therefore, given the breadth of the claims; the lack of guidance and examples; the level of unpredictability in the art; and the state-of-the-art as discussed above, the Examiner concludes that undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled. *Id.*

Appellant's Position

Appellant takes issue with the references cited by the Examiner to support unpredictability in the art and lack of enablement. Appellant argues that the general principles of gene downregulation technologies were known. (App. Br. 31.) Appellant argues that

> [T]he specification at page 16, lines 8-28, page 18, lines 26-28 and pages 30-32, for example, disclose the construction of partial Arabidopsis Metl sequences linked to a female germ line promoter, discloses their usefulness for downregulation and discloses the use of a construct to produce seeds with modified endosperm.

(App. Br. 34-35.) Appellant argues that the Examiner has failed to identify a single reported instance where downregulation of a Metl gene failed to reduce the degree of methylation.

Appellant puts forth the Declaration of Dr. Jacobsen in support of the predictability of the art. (App. Br. 34.)

Jacobsen Declaration

To summarize, the Declarant concludes that the evidence of record supports that one of ordinary skill in the art would have expected hypomethylation in various plants and supports that sequences of less than 100% identity hybridize to methyltransferases.

Cannon

Dr. Jacobsen concludes that one of ordinary skill would have understood from Cannon that "a 41-base pairing homology was sufficient to give up to a 100% inhibition of GUS [gene] expression." Cannon 46. Jacobsen Declaration at ¶ 11.

The Cannon reference also states at page 39 that "antisense RNA has a complementary sequence to mRNA and inhibits gene translation by a mechanism as yet unknown but presumed to involve duplex formation."

Thus, Cannon dealt with inhibition of the GUS gene in plant leaves and roots (Cannon 46) and does not support that the resulting decrease in overall methylation in any plant would predictably result in production of a modified (heavier) endosperm.

Jacobsen and Finnegan

According to Dr. Jacobsen, the Jacobsen 2000 reference concerned

> [T]he observation that the *AGAMOUS* gene was hypermethylated in an *Arabidopsis* line expressing a Metl antisense construct. These lines were previously described as having up to a 90% decrease in overall DNA methylation. Finnegan et al., (1996) Proc. Natl. Acad. Sci. U.S.A. 93:8449. An earlier publication, the Jacobsen 1997 reference, showed that the *SUPERMAN* gene was hypermethylated in the same *Arabidopsis* line expressing a Metl antisense construct, and these experiments also confirmed the simultaneous overall hypomethylation in this line. (Jacobsen et al., Science 1997 277: 1100- 1103).

Jacobsen Declaration at ¶12.

The Jacobsen Declaration indicates that the "observation of hypermethylation of the *SUPERMAN* gene or the *AGAMOUS* gene in *Arabidopsis* Metl antisense construct-containing lines does not change the fact that these lines had a significant reduction in the degree of overall DNA methylation." Appellant argues that "the data about the *SUPERMAN* and *AGAMOUS* genes in the Jacobsen 1997 and 2000 references have no bearing on whether one of ordinary skill would have expected a decrease in the

degree of overall DNA methylation upon downregulation of Metl expression." Jacobsen Declaration at ¶ 14.

We agree with the Examiner and Appellant that Jacobsen 2000 discloses a reduction in the DNA methylation in Arabidopsis (not any plant), but only shows that this decreased methylation results in a changed floral phenotype (Jacobsen 2000 abstract) and does not disclose a change in phenotype in the endosperm or seed, as claimed.

Dr. Jacobsen further concluded that the

> [T]echniques required to screen and identify Metl downregulation construct-containing plants that have a decrease in DNA methylation would have been routine for one of ordinary skill, because the techniques involved would have been typical of those carried out by one of ordinary skill. Such techniques include constructing DNA clones containing partial and full-length *Arabidopsis* or *Zea mays* DNA methyltransferase 1 Metl sequences, constructing plant transformation vectors, transforming plants, and screening for overall DNA methylation status.

Jacobsen Declaration at ¶ 16. Dr. Jacobsen does not address how to predictably alter the phenotype of the endosperm or seed in any plant or evidence that methyltransferase is present in the endosperm of any plant.

Fourgoux-Nicol

According to Dr. Jacobsen, Fourgoux-Nicol shows that hybridization techniques were used successfully to isolate desired clones. Jacobsen Declaration at ¶ 18. Dr. Jacobsen finds that

> The authors of the Fourgoux-Nicol reference focused their analysis on one of the thirteen cDNA clones whose

> expression was strictly confined to the male gametophyte and was high in the microspore. The selected clone was designated M3 and had a length of 497 bp. Fourgoux- Nicol at page 863, left-hand column. M3 was used in a second round of screening by stringent hybridization to isolate a second cDNA clone, designated M3.21. M3.21 has a length of 674 bp. Fourgoux-Nicol at page 863, left-hand column. M3 and M3.21 were sequenced and found to have non-identical sequences, including a 99 base pair insertion in M3 that was not present in M3.21, and several single nucleotide polymorphisms between the two. Fourgoux-Nicol at page 863, right-hand column, and page 862 Figure 2. Further analysis, including Southern hybridization, indicated that the M3 and M3.21 cDNAs were derived from two homologous genes. Fourgoux-Nicol at page 864, left-hand column. Thus, the reference shows that 100% sequence identity is not required in order to successfully isolate related sequences by nucleic acid hybridization.

Jacobsen Declaration at ¶ 19.

> Dr. Jacobsen concludes that
>
> The fact that nucleic acids that do not have 100% DNA sequence identity, such as M3 and M3.21, can hybridize to each other would indicate to one of ordinary skill that hybridization would likely occur between a partial or full length *Arabidopsis* or *Zea mays* DNA methyltransferase 1 Metl sequence and an endogenous DNA methyltransferase 1 Metl target even when there is less than 100% sequence identity.

Jacobsen Declaration at ¶ 20.

While Fourgoux-Nicol supports the position that, in a particular instance with a gene involving male gametophyte development, that nucleic acids that do not have 100% DNA sequence identity can hybridize to each other, it does not provide evidence to address the Examiner's concern that

the hybridization to Met1 in any plant would necessarily result in the desired endosperm, modified phenotype.

Hibino

Dr. Jacobsen finds that Hibino reports that "introduction of an *Aralia cordala* cinnamyl alcohol dehydrogenase (CAD) antisense construct into tobacco resulted in an approximately 20-55% reduction in CAD activity. See page 929 and Figure 1 of Hibino." Jacobsen Declaration at ¶ 22.

Two plants showed a reduction in CAD whereas others showed no significant change, evidencing unpredictability in the art. (Hibino, page 929, col.2.) Thus Hibino dealt with inhibition of the CAD gene and does not support that the resulting decrease in overall methylation in any plant would predictably result in production of a modified endosperm.

Bolitho

Bolitho report that introduction of an apple antisense ACC-oxidase reduced the level of RNA and the activity of the corresponding gene for ethylene production in tomato. *See* Figures 3 and 4 of Bolitho. Jacobsen Declaration at ¶ 22.

Bolitho, however also states that high levels of antisense sequence were not always associated with reduction in ethylene levels evidencing unpredictability in the art. (Abstract.) Thus, Bolitho does not support that a resulting decrease in overall methylation in any plant would predictably result in production of a modified endosperm.

Salehuzzaman

Salehuzzaman report that introduction of a cassava granule bound starch synthase antisense gene suppressed levels of the corresponding protein in potato. *See* Figure 10 in Salehuzzaman. Jacobsen Declaration at ¶ 22.

In Salehuzzaman the gene in question was abundantly expressed in tubers (not endosperm), minimally expressed in petioles and stems and not expressed in roots. (Salehuzzaman, page 955.) Levels of antisense inhibition varied from complete inhibition to no visible effect, evidencing unpredictability in the art. (Salehuzzaman, page 960, col. 2.) Thus, Salehuzzaman does not support that a resulting decrease in overall methylation in any plant would predictably result in production of a modified endosperm.

Elkind

Elkind report that introduction of a bean phenylalanine ammonia-lyase (PAL) sense sequence into tobacco resulted in reduced levels of PAL activity and reduced accumulation of endogenous PAL transcripts. *See* Elkind at page 9059-9060. Jacobsen Declaration at ¶ 22.

Dr. Jacobsen concluded that one of ordinary skill would have expected that, in general, heterologous partial or full length sequences can be used to downregulate endogenous genes based on, inter alia, the successful results reported in the references of paragraph 22, including Elkind.

However, Elkind concludes that transgenic plants can evidence a series of unusual, i.e., unexpected phenotypes, evidencing unpredictability in the art. (Abstract.) Expression of phenotype is also affected by the environment. (Elkind, page 9059.) Thus, Elkind does not support that a

resulting decrease in overall methylation in any plant would predictably result in production of a modified endosperm.

Emery[3]

Emery looked at the function of HD-ZIP and KANADI genes in the meristem of plants with respect to adaxial and abaxial leaf production. The authors found five class III HDZIP genes in Arabidopsis and that they have diversified common and unique functions. (Emery 1771, col. 2.) Jacobsen Declaration at ¶ 25. Dr. Jacobsen concluded that one of ordinary skill, after reviewing the Emery reference, would not conclude that use of antisense techniques in plant molecular biology requires a 100% sequence match between an introduced sequence and its target.

While the Emery reference reports that mismatches introduced within microRNA target sites can abolish mRNA function, such a result does not mean that sequences with imperfect homology would necessarily be ineffective for downregulation. Jacobsen Declaration at ¶ 25.

Thus, Emery does not support that the resulting decrease in overall methylation in any plant would predictably result in production of a modified endosperm.

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[3] Appellant argues that Emery is a post filing date reference that has no evidence of what one skilled in the art would have known on or before the effective filing date. Therefore, the Emery reference is not relevant to whether the claimed invention would have been enabled as of the effective filing date. Appellant argues that Emery actually demonstrates the precision with which one of ordinary skill can upregulate or downregulate a particular gene. (App. Br. 33-34.)

Gutterson

Dr. Jacobsen found after reviewing the Gutterson reference, that one of ordinary skill in the

> would not conclude that use of sense suppression techniques in plant molecular biology requires a 100% sequence match between an introduced sequence and its target. While the Gutterson reference reports that a chrysanthemum chalcone synthase sense sequence did not suppress a petunia chalcone synthase, such a result does not mean that sequences with imperfect homology would necessarily be ineffective for downregulation.

Jacobsen Declaration at ¶ 27.

Gutterson also discloses that the proportion of plants with high levels of suppression decreased with decreasing fragment length. (Gutterson 965, col. 2.) Thus, Gutterson does not support that a resulting decrease in overall methylation in any plant would predictably result in production of a modified endosperm.

Other evidence

Appellant further argues that the complete carrot, corn, pea and tomato Metl sequences were known from the earliest priority date from Genbank Accession Numbers AF007807, AF063403, AF034419 and AJ002140. Evidence Appendices G, F, H, and I. Appellant argues that there are numerous regions in these sequences that are highly conserved even though *Zea mays* is a monocot and the remainder are dicots, directing one of ordinary skill to partial *Arabidopsis* Metl sequences that would have been effective for downregulation in heterologous species. (App. Br. 19-20.)

While these references support that the Met1 sequences of other plants were known, they do not evidence that a resulting decrease in overall methylation in any plant would predictably result in production of a modified endosperm.

"Applicant submitted eight additional references that report downregulation using heterologous sequences, including sequences having less than 100% sequence identity to an endogenous gene. Evidence Appendix N."[4] According to Appellants, "[t]hese other prior art references show one of ordinary skill would have concluded that antisense sequences with less than 100% sequence identity can be used to downregulate a heterologous endogenous gene." (App. Br. 34.)

These references are purported to evidence downregulation using heterologous sequences, including sequences having less than 100% sequence identity to an endogenous gene. However, Oliver discloses that the production of heterologous hydroxypyruvate reductase (HPR) RNA did not systematically reduce levels of tobacco HPR. (Oliver, Abstract.) VanderKrol discloses that the pattern of plant pigmentation derived from the flavonoid biosysnthesis pathway varies among flowers of different

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transgenic plants indicating that the antisense gene is influenced by DNA sequences that border the site of insertion in both a quantitative and qualitative way. (VanderKrol, Abstract.) Carron indicates that downregulation of tannin biosynthesis is dependent upon Lotus genotype. (Carron, Abstract.) Einset discloses that there is differential expression of antisense genes involving ethylene production. Ethylene production in flowers was not effected but ethylene production in fruits was inhibited. (Einset, Abstract.) Thus, the cited references do not evidence that a resulting decrease in overall methylation in any plant would predictably result in production of a modified endosperm, and support a level of unpredictability in the art.

Wands Factors

With respect to the *Wands* factors, Appellant argues that the Specification states in the context of decreasing the degree of methylation that "the transgene can incorporate sequences which cause down regulation of methylating enzymes already present in the plant, and states that '[for example, one can use antisense sequences, e.g., the Metlas 'gene'." Specification at page 18, lines 26-28. (App. Br. 13.)

Second, Appellant argues that the present specification indicates the inventor considered part of the invention to be the use of a female germ line promoter to downregulate DNA methyltransferases.

For example, the Specification indicates that

> [e]xpression of the MET1 gene can be reduced in the female or male germ lines by employing techniques known in the art. For example MET1 down-regulation can be achieved by expressing antisense MET1 or antisense MET 1 fragments or sense MET1

> or partial sense METl or ribozymes directed against MET1 or combinations of the preceding, from promoters expressed in the required germ-line. Specification at page 30, lines 15-19.

Id.

Third, Appellant argues that the Specification "discloses a working example using a partial Metl sequence. Example 3 describes the preparation of a construct having a partial Arabidopsis Metl antisense sequence targeted to the female germ line. Example 4 describes its use to produce modified endosperm. Examples 3-4, pages 30-32." (App. Br. 13.)

> Fourth, the Arabidopsis Metl sequence was known in the art. See, e.g., Finnegan et al., Nucleic Acids Res. 23:2383-2388 (1993). Evidence Appendix B. The specification indicates that the Arabidopsis Met1 sequence is published as Accession No. L10692. The specification indicates that "down-regulation can be achieved by expressing antisense MET1 or antisense MET1 fragments or sense MET1 or partial sense METl or ribozymes directed against MET1 or combinations of the preceding, from promoters expressed in the required germ-line." Specification at page 30, lines 16-19. Rather than mechanically reciting partial Arabidopsis Met1 sequences in the specification, Applicant referred to partials of the known sequence because one of ordinary skill would have easily visualized the identity of partial Arabidopsis Metl sequences based on the full-length sequence. That is, a partial or full-length Arabidopsis Metl sequence is not a new or unknown biological material that one of ordinary skill would easily miscomprehend. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003).

(App. Br. 13-14.)

Appellant concludes that, in view of the specific recitation of the Arabidopsis Metl sequence in the claim, the guidance provided in the Specification, and the evidence presented in the Jacobsen Declaration, no

more than routine experimentation would have been required to practice the full scope of the claim. (App. Br. 33.)

The Examiner does not find the evidence of record convincing of enablement or lack of undue experimentation because the evidence does not support that the resulting decrease in overall methylation in a plant would predictably result in production of a modified endosperm. (Final Rej. 8.)

Reviewing the evidence anew, we find that a preponderance of the evidence before us supports the finding that the state of the art is unpredictable and that more disclosure is required to enable and support the down regulation of Met1 in **any plant** to produce **a modified endosperm**. (FF 21, 22, 35, 36, 38, 41, 46, 47, 48, and 49.) In particular, we find that the evidence before us shows that down regulation of plant genes often has an effect on one portion of a plant and not other portions of a plant. Down regulation of a plant gene may affect a tuber, root, flower, or endosperm in an unpredictable manner.

Separately argued claims[5]

On pages 35 to 37 of the Brief, Appellant separately argues claims 21, 64, 65, 66, 67, 71, 77, 78, 80, 81, and 82. These claims also broadly cover downregulation of Met1 in any plant and therefore fall for the same reasons indicated herein.

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[5] Appellant attempts to argue claims 63, 69, 76, and 86-93 separately by simply listing their limitations (App. Br. 45-47). Technically, this does not constitute a separate argument under 37 C.F.R. 41.37(c)(1)(vii) ("A statement which merely points out what a claim recites will not be considered an argument for separate patentability of the claim.").

Claims 83, 84, 91 and 92

Appellant contends that Examples 3 and 4 of the Specification describe transformation of *Arabidopsis thaliana*, a member of the Brassicaceae family. (App. Br. 38.) The Examiner admits on page 7 of the Answer that the Specification is enabling for increasing the amount of endosperm in an Arabidopsis or Brassica seed. Therefore, the enablement rejection of claims 83, 84, 91 and 92 are reversed.

Claim 85

Appellant traverses this rejection for the same reasons given for claims 77 and 82. (App. Br. 39.) The Specification does not exemplify transformation of a plant of the *Zea may*s species. For the reasons given herein for claims 20, 77 and 82, we affirm the rejection of claim 85.

In view of the weight of the evidence, the lack of enablement rejection for all claims (except claims 83, 84, 91 and 92) is affirmed.

3. Claims 20-21, 62-67, 69, 71, 76-78, 80-93 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such away as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

ISSUE

The Examiner argues that "[a]ppellant does not identify essential regions of the *Arabidopsis* Metl sequence, nor any partial sequences thereof, nor any partial sequence of the *Zea mays* orthologue of the *Arabidopsis* Metl

sequence, that can be used to down-regulate one or more methylating enzymes present in any plant." (Ans. 5.) The Examiner further argues that Appellant does not disclose any sequence whose transcription product is a **partial** *Arabidopsis* Met 1 or *Zea mays* orthologous sequence to the *Arabidopsis* Met1 sequence. (Ans. 5.)

Appellant contends that

> [T]he evidence above and the record as a whole strongly support a conclusion that the present specification provide more than adequate written description for the pending claims to one of ordinary skill in the art.

(App. Br. 27.)

The issue is: Does the evidence above and the record as a whole demonstrate that one of ordinary skill would understand that Appellant has describe the invention in the full scope claimed, that is production of a modified endosperm in any plant.

PRINCIPLES OF LAW

> The 'written description' requirement . . . serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. . . .
>
> The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.

Capon v. Eshhar, 418 F.3d 1349, 1357 (Fed. Cir. 2005). The law must be applied to each invention that enters the patent process, for each patented

advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science. It is well recognized that in the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining the scope of the coverage to which the inventor is entitled. Such a decision usually focuses on the exemplification in the specification. *See, e.g., Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002).

With respect to the written description requirement, while "examples explicitly covering the full scope of the claim language" typically will not be required, a sufficient number of representative species must be included "to demonstrate that the patentee possessed the full scope of the [claimed] invention." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005).

The court has since clarified that the complete structure of the representative species does not necessarily have to be described. *See Enzo*, 323 F.3d at 964-65. However, a correlation between the claimed function and structure must be "*known or disclosed.*" *Id.* at 964 (citing with approval PTO's Guidelines, 66 Fed. Reg. at 1106).

ANALYSIS

The Examiner finds that

> Appellant fails to describe a representative number of sequences whose transcription product is a partial sequence of the *Arabidopsis* Metl sequence, or partial sequences of the *Zea mays* homologue of the *Arabidopsis* Metl sequence, that can be

> used to down-regulate one or more methylating enzymes in any plant. Furthermore, Appellant fails to describe structural features common to members of the claimed genus of polynucleotides. Hence, Appellant fails to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements of said sequences that can be used to down-regulate any methylating enzyme in any plant, it remains unclear what features identify an *Arabidopsis* Metl sequence or identify the *Zea mays* homologue of the *Arabidopsis* Metl sequence, or what sequences can be used to identify partial sequences of the *Arabidopsis* Metl or partial sequences of the *Zea mays* homologue of the *Arabidopsis* Metl sequence. Since the genus of said sequences has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

(App. Br. 6.)

Appellant's arguments do not persuade us that the Examiner erred in finding that the claims lack descriptive support.

"The descriptive text needed to meet the written description varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon*, 418 F.3d at 1357. The application of the written description requirement varies with differences in the state of knowledge in the field and differences in the predictability of the science. It is well recognized that in the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining the scope of the coverage to which the inventor is entitled. Such a decision usually focuses on the exemplification in the specification.

We found with respect to the enablement rejection that the state of the art is unpredictable regarding the ability to down regulate MET1 in any

plant. Appellant has failed to provide evidence that one of ordinary skill in the art was aware that Met1 is present in the endosperm of any plant type or that a full or partial antisense sequence to Met1 would result in a modified endosperm.

Similarly, we find with respect to the written description rejection that in this unpredictable field of science that additional exemplification in the Specification is required to describe modification of endosperm in any plant as claimed. Thus, given the disclosure of a single species of *Arabidopsis* Met1 sequence, shown only to be capable of modifying endosperm production in one plant species, we agree with the Examiner that the disclosure as filed does not adequately demonstrate possession of the claimed genus encompassing all partial sequences that act to modify the endosperm of any plant.

Separately argued claims[6]

On pages 17 to 20 of the Brief, Appellant separately argues claims 21, 64, 65, 66, 67, 71, 77, 78 80, 81, and 82. These claims also broadly cover downregulation of Met1 in any plant, which has not been exemplified or described in the Specification, and therefore fall for the same reasons indicated herein.

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[6] Appellant attempts to argue claims 63, 69, 76, and 86-93 separately by simply listing their limitations (App. Br. 25-27). Technically, this does not constitute a separate argument under 37 C.F.R. 41.37(c)(1)(vii) ("A statement which merely points out what a claim recites will not be considered an argument for separate patentability of the claim.").

Claims 83, 84, 91 and 92

Appellant contends that Examples 3 and 4 of the Specification describe transformation of *Arabidopsis thaliana*, a member of the Brassicaceae family. (App. Br. 20.) While this may be true, the Specification does not describe the structures of those members of the genus of partial sequences that act to modify the endosperm of the claimed plants. We therefore agree with the Examiner that the single species of Met1 sequence is insufficient to show possession of the entire genus, even with respect to these claims. Thus, the written description rejection of claims 83, 84, 91 and 92 is affirmed.

Claim 85

Appellant traverses this rejection for the same reasons given for claims 77 and 82. (App. Br. 39.) The Specification does not exemplify transformation of a plant of the *Zea mays* species. For the reasons given herein for claims 20, 77 and 82, we affirm the written description rejection of claim 85.

In view of the weight of the evidence, the lack of written description rejection for all claims (except claims 83, 84, 91 and 92) is affirmed.

SUMMARY

The indefiniteness rejections are reversed. The enablement and lack of written description rejections are affirmed except, that the enablement rejections of claims 83, 84, 91, and 92 are reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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